11. (Amended) A method of preventing inflammatory bowel disease in a subject, comprising administering to the subject a monoclonal antibody to αEβ7.

21. (Amended) The method of claim 1, further comprising administering a monoclonal antibody to α4β7.

26. (Amended) The method of claim 11, further comprising administering a monoclonal antibody to α4β7.

Please cancel claims 2-7, 10, 12-17, 20, 22-23 and 27-28 without prejudice.

REMARKS

Claims 1-43 are pending in the present application. Claims 2-7, 10, 12-17, 20, 22-23 and 27-28 are canceled herein without prejudice. Claims 1, 11, 21 and 26 are amended herein. Support for the amendments to claim 1 can be found in claims 1-4 as filed and throughout the specification. Support for the amendments to claim 11 can be found in claims 11-14 as filed and throughout the specification. Support for the amendments to claim 21 can be found in claims and 22-23 as filed as well as throughout the specification. Support for the amendments to claim 26 can be found in claims 11, 27-28 as filed and throughout the specification. No new matter is believed to be added by these amendments. In light of these amendments and the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Objection to Abstract

The Office Action states that the application does not contain an abstract of the disclosure as required by 37 C.F.R.§ 1.72(b). Therefore, an abstract on a separate sheet is required.

Applicants provide herewith, on a separate sheet, an abstract of the disclosure as required by 37 C.F.R. § 1.72(b). Therefore, applicants believe this objection has been overcome and respectfully request its withdrawal.

II. Rejections Under 35 U.S.C. § 112, first paragraph

A. The Office Action states that claims 1-7, 10-17, 20-23 and 26-28 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of treating inflammation associated with inflammatory bowel disease with αEβ7 Mab and further comprising administering an α4β7 Mab allegedly does not reasonably provide enablement for a method of treating any inflammation in a subject comprising any antagonist to αEβ7 in claim 1, wherein the antagonist is any antibody in claim 2, wherein the inflammation is associated with asthma, rheumatoid arthritis, autoimmune diseases, or graft vs. host diseases in claims 5-7 and 10 and further comprising another therapeutic agent in claim 21, wherein the other therapeutic agent is any antibody in claim 22. The Office Action also states that a method of preventing inflammation in a subject, comprising administering to the subject any antagonist to αEβ7 in claim 11, wherein the antagonist is any antibody in claim 12, wherein the antibody is an αEβ7 Mab and wherein the inflammation is associated with an inflammatory bowel disease, asthma, rheumatoid arthritis, autoimmune diseases and host vs. graft disease in claims 14-17 and 20 is allegedly not enabled. Further stated in the Office Action is that the method further comprising administering another therapeutic agent in claim 26, wherein the other therapeutic agent is any antibody in claim 27, and wherein the antibody is α4β7 in claim 28 is allegedly not enabled.

The Office Action also states that also at issue is whether or not the claimed method would function for "the treatment/the prevention" of inflammation associated with asthma, rheumatoid arthritis, autoimmune disease and graft vs. host disease or the prevention of inflammation associated with inflammatory bowel disease. The nature of the invention is such that it would require the administration of anti-αEβ7 and anti- α4β7 that would prevent a subject from inducing colitis. The exemplification is drawn to decrease in the severity of the colitis in an IL-2 -/- mouse model, as indicated by the reduction in colitis severity score to demonstrate the ability of the anti- αEβ7 to block colitis. Further stated in the Office Action is that since mice were used as an animal model system to reduce the severity of colitis, such animal model studies have not correlated well with *in vivo* clinical trial results in patients.

According to the Office Action, since the method of preventing indices of administering to the animal anti- αEβ7 and further anti- α4β7 can be species and model dependent, it is not clear that reliance on the mice studies accurately reflects the relative human efficacy of the claimed therapeutic strategy. The specification allegedly does not adequately teach how to effectively "treat"/"prevent" inflammation associated with asthma, rheumatoid arthritis, autoimmune disease and graft versus host disease or the prevention of inflammation associated with inflammatory bowel disease or reach any therapeutic endpoint in subjects by administering anti- αEβ7 and further anti- αEβ7. The specification does not teach how to extrapolate data obtained from mice studies to the development of effective *in vivo* mammalian therapeutic prevention/treatment, commensurate in scope with the claimed invention. The Office Action also states that there is insufficient guidance in the specification as to how to determine the subject in whom prevention is desired versus those in whom it is not desired.

Claims 2-7, 10, 12-17, 20, 22-23 and 27-28 are canceled herein. The remaining claims, e.g. 1, 11, 21 and 26, are directed to inflammatory bowel disease. Claim 1 is amended herein to recite a method of treating inflammatory bowel disease in a subject, comprising administering to the subject a monoclonal antibody to αEβ7. Similarly, claim 11 is amended to recite a method of preventing inflammatory bowel disease in a subject, comprising administering to the subject a monoclonal antibody to αEβ7. Claim 21 is also amended herein to recite the method of claim 1, further comprising administering a monoclonal antibody to α4β7. Similarly, claim 26 is amended herein to recite the method of claim 11, further comprising administering a monoclonal antibody to α4β7.

The Examiner has stated that the specification is enabling for a method of treating inflammation associated with inflammatory bowel disease with αEβ7 Mab and further comprising administering an α4β7 Mab. Therefore, applicants believe that this rejection, as it applies to claims 1 and 21, has been overcome and respectfully request its withdrawal.

Applicants respectfully disagree with the Examiner's statement that a method of preventing inflammation in a subject, comprising administering to the subject an αEβ7 Mab, wherein the inflammation is associated with an inflammatory bowel disease is not enabled.

Applicants have clearly shown that administration of an αEβ7 Mab is effective for both treatment and prevention of inflammatory bowel disease. Specifically, in the paragraph bridging pages 19-20, the specification describes how IL-2-/- mice maintained under specific pathogen-free condition were immunized with TNP-OVA and given either anti-$\alpha^E\beta_7$ or anti-$\alpha_4\beta_7$ mAbs at the same time of immunization. Therefore, colitis was induced in IL-2-/- mice that were maintained in specific pathogen-free environment and the effects of concomitant injection of $\alpha^E\beta_7$ mAb were evaluated. As shown in Figure 1, severe colitis was seen in mice injected with TNP-OVA, however, when TNP-OVA was co-injected with anti-$\alpha^E\beta_7$ mAb the colitis was prevented and microscopic examination of the colonic mucosa resembled the one seen in PBS-injected mice. This was reflected by significant reduction in colitis severity score (CSS); IL-2-/- mice injected with TNP-OVA, CSS: 3-4 vs. TNP-OVA + anti-$\alpha^E\beta_7$ injected, CSS: 0-2 (Table1). Furthermore, this inhibition of colitis was associated with a fourfold reduction in LPL numbers and twofold reduction in IEL numbers in mice that were co-injected with $\alpha^E\beta_7$ mAb (IL-2-/- LPL: TNP-OVA; $180\pm5 \times 10^6$ vs. TNP-OVA co-injected with anti-$\alpha^E\beta_7$ $6.5\pm0.6 \times 10^6$. IL-2-/- IEL: TNP-OVA; $5.2\pm1.8 \times 10^6$ vs. TNP-OVA co-injected with anti-$\alpha^E\beta_7$; $2.4\pm0.9 \times 10^6$).

Furthermore, on page 10, lines 16-26, the specification states that "the efficacy of an antagonist of $\alpha^E\beta_7$ in preventing an autoimmune disease, allergic disease, GvH disease or transplantation rejection in a subject not known to have an autoimmune disease, allergic disease, GvH disease or transplantation rejection can be determined by evaluating standard signs, symptoms and objective laboratory tests, as would be known to one of skill in the art, over time. This time interval may be large, with respect to the development of an autoimmune disease or allergic disease (years/decades) or short (weeks/months) with respect to the development of GvH disease or transplantation rejection. The determination of who would be at risk for the development of an autoimmune disease or allergic disease would be made based on current knowledge of the known risk factors for a particular disease familiar to a clinician in this field, such as a particularly strong family history of disease." Therefore, with regard to determining which subjects are in need of preventive treatment, one of skill in the art would clearly know how to assess the risk factors associated with a particular subject and monitor the subject such

that therapy for prevention of an autoimmune disease, such as inflammatory bowel disease, can be administered.

Thus, applicants believe that applicants have clearly taught how to prevent inflammatory bowel disease by administering an antibody to αEβ7. Therefore, applicants believe that claims 11 and 26 are adequately enabled and respectfully request withdrawal of this rejection.

B. The Office Action states that claims 1-7, 10-17, 20-23 and 26-28 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

According to the Office Action, applicant is in possession of a method of treating inflammation associated with inflammatory bowel disease, with the αEβ7 Mab and further comprising administering an α4β7 Mab. Further stated in the Office Action, is that applicants were not in possession of a method of treating any inflammation in a subject comprising any antagonist to αEβ7. The Office Action also alleges that applicants were not in possession of a method of preventing inflammation in a subject comprising administering to the subject an antagonist to αEβ7.

As stated above, claims 2-7, 10, 12-17, 20, 22-23 and 27-28 are canceled herein. The remaining claims, e.g. 1, 11, 21 and 26, are directed to inflammatory bowel disease. Claim 1 is amended herein to recite a method of treating inflammatory bowel disease in a subject, comprising administering to the subject a monoclonal antibody to αEβ7. Similarly, claim 11 is amended to recite a method of preventing inflammatory bowel disease in a subject, comprising administering to the subject a monoclonal antibody to αEβ7. Claim 21 is also amended herein to recite the method of claim 1, further comprising administering a monoclonal antibody to α4β7. Similarly, claim 26 is amended herein to recite the method of claim 11, further comprising administering a monoclonal antibody to α4β7.

The Examiner has stated that applicants are in possession of a method of treating inflammation associated with inflammatory bowel disease with αEβ7 Mab and further comprising administering an α4β7 Mab. Therefore, applicants believe that this rejection, as it applies to claims 1 and 21, has been overcome and respectfully request its withdrawal.

Applicants respectfully disagree with the Examiner's statement that applicants were not in possession of a method of preventing inflammation in a subject, comprising administering to the subject an αEβ7 Mab.

As stated above, applicants have clearly shown that administration of an αEβ7 Mab is effective for both treatment and prevention of inflammatory bowel disease. Specifically, in the paragraph bridging pages 19-20, the specification describes how IL-2-/- mice maintained under specific pathogen-free condition were immunized with TNP-OVA and given either anti-$\alpha^E\beta_7$ or anti-$\alpha_4\beta_7$ mAbs at the same time of immunization. Therefore, colitis was induced in IL-2-/- mice that were maintained in specific pathogen-free environment and the effects of concomitant injection of $\alpha^E\beta_7$ mAb were evaluated. As shown in Figure 1, severe colitis was seen in mice injected with TNP-OVA, however, when TNP-OVA was co-injected with anti-$\alpha^E\beta_7$ mAb the colitis was prevented and microscopic examination of the colonic mucosa resembled the one seen in PBS-injected mice. This was reflected by significant reduction in colitis severity score (CSS); IL-2-/- mice injected with TNP-OVA, CSS: 3-4 vs. TNP-OVA + anti-$\alpha^E\beta_7$ injected, CSS: 0-2 (Table1). Furthermore, this inhibition of colitis was associated with a fourfold reduction in LPL numbers and twofold reduction in IEL numbers in mice that were co-injected with $\alpha^E\beta_7$ mAb (IL-2-/- LPL: TNP-OVA; 180±5 x 10^6 vs. TNP-OVA co-injected with anti-$\alpha^E\beta_7$ 6.5±0.6 x 10^6. IL-2-/- IEL: TNP-OVA; 5.2±1.8 x 10^6 vs. TNP-OVA co-injected with anti-$\alpha^E\beta_7$; 2.4±0.9 x 10^6).

Furthermore, on page10, lines 16-26, the specification states that "the efficacy of an antagonist of $\alpha^E\beta_7$ in preventing an autoimmune disease, allergic disease, GvH disease or transplantation rejection in a subject not known to have an autoimmune disease, allergic disease, GvH disease or transplantation rejection can be determined by evaluating standard signs, symptoms and objective laboratory tests, as would be known to one of skill in the art, over time.

This time interval may be large, with respect to the development of an autoimmune disease or allergic disease (years/decades) or short (weeks/months) with respect to the development of GvH disease or transplantation rejection. The determination of who would be at risk for the development of an autoimmune disease or allergic disease would be made based on current knowledge of the known risk factors for a particular disease familiar to a clinician in this field, such as a particularly strong family history of disease." Therefore, with regard to determining which subjects are in need of preventive treatment, one of skill in the art would clearly know how to assess the risk factors associated with a particular subject and monitor the subject such that therapy for prevention of an autoimmune disease, such as inflammatory bowel disease, can be administered.

Therefore, applicants believe that applicants have adequately described and shown how to prevent inflammatory bowel disease by administering an antibody to αEβ7 and thus, were in possession of a method of preventing inflammatory bowel disease by administering an antibody to αEβ7 . Therefore, applicants believe that claims 11 and 26 are adequately described and respectfully request withdrawal of this rejection.

III. Rejections Under 35 U.S.C. § 102(b)

A. The Office Action states that claims 1, 4, 5, 7, 10, 11, 14, 15, 17 and 20 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5, 610,281. According to the Office Action, the '281 teaches a method for treatment, i.e. reduction or prevention of autoimmune disease, which is characterized by inflammation. The treatment comprises the administration of an isolated peptide derived from the extracellular domain of E-cadherin, which binds to αEβ7 and inhibits the adhesion between an IEL and E-cadherin. The '281 patent teaches the treatment of ulcerative colitis, asthma and graft vs. host disease.

As stated above, claim 1 is amended herein to recite a method of treating inflammatory bowel disease in a subject, comprising administering to the subject a monoclonal antibody to αEβ7. Similarly, claim 11 is amended to recite a method of preventing inflammatory bowel disease in a subject, comprising administering to the subject a monoclonal antibody to αEβ7.

Claims 4, 5, 7, 10, 14, 15, 17 and 20 are canceled herein without prejudice. As amended herein, claims 1 and 11 specifically refer to a monoclonal antibody to αEβ7. Since U.S. Patent No. 5,610,281 does not teach the use of a monoclonal antibody to αEβ7 to treat or prevent inflammatory bowel disease, this reference does not anticipate the present invention. Thus, applicants respectfully request withdrawal of this rejection.

B. The Office Action states that claims 1-3, 7, 11-13 and 17 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,146,630. The '630 patent teaches a method for treating and preventing autoimmune adenitis using anti-integrin αEβ7 antibody wherein the antibodies can be monoclonal or polyclonal.

As stated above, claim 1 is amended herein to recite a method of treating inflammatory bowel disease in a subject, comprising administering to the subject a monoclonal antibody to αEβ7. Similarly, claim 11 is amended to recite a method of preventing inflammatory bowel disease in a subject, comprising administering to the subject a monoclonal antibody to αEβ7. Claims 2-3, 7, 12-13 and 17 are canceled herein without prejudice. As amended herein, claims 1 and 11 specifically refer to treatment of inflammatory bowel disease with a monoclonal antibody to αEβ7. Since U.S. Patent No. 6,146,630 does not teach the use of a monoclonal antibody to αEβ7 to treat or prevent inflammatory bowel disease, this reference does not anticipate the present invention. Thus, applicants believe this rejection has been overcome and respectfully request its withdrawal.

IV. Rejections Under 35 U.S.C. § 103(a)

A. The Office Action states that claims 1, 6, 11 and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5, 610,281, in view of Baumgart et al. According to the Office Action, Baumgart et al. teach the increase in the expression of αEβ7 that is characteristic of intestinal intraepithelial lymphocytes on T cells in tissues affected by inflammation, partly attributable to an autoimmune disease such as synovial fluid of patients with rheumatic diseases. Baumgart et al. further teach that αEβ7 can function as an adhesion/retention molecule wherein the expression of αEβ7 can account for T cell adhesion to the epithelium. Finally, Baumgart et al. teach that the migration of αEβ7/CD8+ T cells can

provide a population of activated cells valuable for defense as participants in inflammation throughout the body. The Office Action concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to target the αEβ7 expressing T cells in the synovial fluid taught by Baumgart et al. using the extracellular domain of E-cadherin derived peptide taught by the '281 patent to prevent the adhesion/retention of IEL into the synovial HEV and home to synovial membrane, therefore, treating and preventing inflammation associated with the rheumatoid arthritis. Further stated in the Office Action is that one of ordinary skill in the art at the time the invention was made would have been motivated to do so because such peptide can reduce the number of infiltrating T cells within the lamina propia lymphocytes (LPL) with high expectation of success in treating inflammation associated with rheumatoid arthritis.

Claims 6 and 16 are canceled herein without prejudice. Claim 1 is amended herein to recite a method of treating inflammatory bowel disease in a subject, comprising administering to the subject a monoclonal antibody to αEβ7. Similarly, claim 11 is amended to recite a method of preventing inflammatory bowel disease in a subject, comprising administering to the subject a monoclonal antibody to αEβ7.

Applicants respectfully point out that the '281 patent teaches the administration of an isolated peptide derived from the extracellular domain of E-cadherin, which binds to αEβ7 and inhibits the adhesion between an IEL and E-cadherin. The disclosure of an interaction between αEβ7 and E-cadherin does not necessarily mean that administering a monoclonal antibody against αEβ7 would be successful in treating or preventing inflammatory bowel disease. In support of this assertion, applicants provide herewith as Exhibit A, the Declaration of Dr. Eugene C. Butcher, a Professor in the Department of Pathology at Stanford University (curriculum vitae attached hereto), whereby Dr. Butcher declares that it is his belief that although the '281 patent discloses the administration of an isolated peptide derived from the extracellular domain of E-cadherin, which binds to αEβ7 and inhibits the adhesion between an IEL and E-cadherin, this interaction between αEβ7 and E-cadherin is not relevant to the present claims, because E-cadherin is expressed in epithelial cells and is not expressed to any appreciable extent in non-epithelial cells of the gut, such as the lamina propia, where inflammatory bowel disease

manifests itself (Strauch et al. "Integrin αEβ7 Mediates Adhesion to Intestinal Microvascular Endothelial Cell Lines Via an E-Cadherin-Independent Interaction" *J. Immunol.* 166: 3506-3514, 2001; Hanby et al. "Downregulation of E-Cadherin in the Reparative Epithelium of the Human Gastrointestinal Tract" *Am. J. Pathol.* 148:723-9, 1996; Cepek et al. "Integrin αEβ7 mediates adhesion of T-lymphocytes to epithelial cells" *J. Immunol.* 150:3459, 1993; Cepek et al. "Adhesion between epithelial cells and T lymphocytes mediated by E-cadherin and the αEβ7 integrin" *Nature* 372:190, 1994; Karcela et al. "Recognition of E-cadherin on epithelial cells by the mucosal T cell integrin αM290β7 (αEβ7)" *Eur. J. Immunol.* 25:852, 1995; Higgins et al. "Direct and regulated interaction of integrin αEβ7 with E-cadherin" *J. Cell Biol.* 140:197, 1998; copies attached hereto). Therefore, the suggestion that the interaction between αEβ7 and E-cadherin can be inhibited to treat inflammatory bowel disease is not supported by the longstanding understanding of E-cadherin expression and mechanisms of inflammatory bowel disease. His belief is based on the following scientific facts and observations.

Dr. Butcher states that although E-cadherin has been identified as an αEβ7 ligand, this is not the only ligand for αEβ7. αEβ7, like other integrins, binds to more than one ligand. For example, the I-domain containing integrin, aMb2(Mac 1), binds a wide repertoire of ligands, including ICAM-1, fibrinogen, iC3b, factor X, denatured proteins, neutrophil inhibitory factor, lipopolysaccahride and zymosan. Yalamanchili et al. (*J. Biol. Chem.* 275: 21377, 2000) have shown that the I-domain is required for binding to some ligands and not others. Similarly, another integrin, α4β7, has multiple ligands, including MadCAM-1, VCAM-1 and fibronectin. Monoclonal antibodies have been generated that define unique patterns of inhibition for α4β7 binding to each of its defined molecular ligands (Andrew DP, *J. Immunol.* 153:3847, 1994). Yet another example is the α3β1 integrin which binds collagen, laminin and fibronectin. However, only the binding of α3β1 integrin to fibronectin, not the binding of α3β1 integrin to laminin or collagen, can be inhibited by RGD-containing peptides (Elices, MJ, *J. Cell Biol.* 112:169, 1991). The αEβ7 integrin is distinct from other integrins in containing both an I-domain and an X domain of 55 amino acids. Binding of alphaE to E-cadherin does not appear to involve the X domain and it is believed that the X domain may be involved in interactions with yet unidentified αEβ7 ligands (Higgins et al. J. Biol. Chem. 275:25662, 2000). Therefore, it is well accepted that

an inhibitor of a ligand for a particular integrin is not expected to be an inhibitor of all of the ligands which bind to that integrin.

It is also known that E-cadherin is not expressed to any appreciable extent in the lamina propia of the gut. Therefore, it is highly unlikely that inflammatory bowel disease is mediated via an αEβ7-E-cadherin interaction. The publication by Strauch et al. ("Integrin alpha E(CD103)beta 7 mediates adhesion to intestinal microvascular endothelial cell lines (HIMEC) via an E-cadherin-independent interaction," *J. Immun.* 166: 3506-3514, 2001) reports that αEβ7 mediates adhesion to intestinal endothelial cells in the lamina propia *in vivo*, via an E-cadherin-independent interaction. Strauch et. al. also suggest the presence of a second ligand for αEβ7 that is clearly distinct from E-cadherin and with a different expression pattern. This reference also showed that a mAb that blocks E-cadherin mediated cell binding to αEβ7, did not block binding of HIMEC to an αEβ7-Fc. Furthermore, HIMEC did not express detectable levels of E-cadherin.

Another reference has suggested that αEβ7 mediates lymphocyte binding to a skin-derived epithelial cell line through an E-cadherin independent interaction (Brown et al. "Mechanisms of binding of cutaneous lymphocyte-associated antigen-positive and alphaebeta7-positive lymphocytes to oral and skin keratinocytes" *Immunology* 98:9-15, 1999). Further evidence that αEβ7 can have a different, E-cadherin independent role in cell homing and inflammation comes from gene expression analysis showing that αEβ7 is expressed on T cell populations outside the intraepithelial area, e.g. in areas that do not contain E-cadherin expressing cells (Gavin M. et al., "Homeostasis and anergy of CD4(+)CD25(+) suppressor T cells in vivo" *Nat. Immunol.*, 3(1):33, 2002; Zelenika D., "Regulatory T cells overexpress a subset of Th2 gene transcripts" *J. Immunol.* 168(3): 1069, 2002; McHugh RS et al., "CD4(+)CD25(+) immunoregulatory T cells: gene expression analysis reveals a functional role for the glucocorticoid-induced TNF receptor" *Immunity* 16(2):311, 2002).

Therefore, it would not be expected that the identification of an inhibitor of E-cadherin binding to αEβ7, would provide an inhibitor for the interaction of αEβ7 with another ligand, such as the ligand involved in inflammatory bowel disease. Although the '281 patent discloses that administration of an E-cadherin peptide leads to decreased localization of intra-epithelial lymphocytes to the intraepithelial compartment, the '281 patent does not show or suggest that an αEβ7 Mab will inhibit binding of αEβ7 to another ligand or that an αEβ7 Mab will inhibit any activity associated with the interaction of αEβ7 with a non-E cadherin ligand. Furthermore, because E-cadherin is not found at appreciable levels in the lamina propia, it would not be likely that an E-cadherin based mechanism would be successful for treatment of inflammatory bowel disease, and it would not have been obvious, at the time the present invention was made, to target an E-cadherin ligand, e.g. αEβ7, to treat inflammatory bowel disease. Therefore, it would not be obvious to combine the teachings of the '281 patent with those of Baumgart et al. to arrive at the present invention. Thus, applicants believe that this rejection has been overcome and respectfully request its withdrawal.

B. The Office Action states that claims 1-7, 10, 11-17, 20-23 and 26-28 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,610,281, in view of U.S. Patent No. 6,146,630, Baumgart et al. and Hesterberg et al. (1997). The teachings of the '281 patent, the '630 patent and Baumgart et al. are discussed above. The Office Action also states that Hesterberg et al. teach a method of ameliorating and treating an animal with chronic colitis with α4β7 Mab. Hesterberg et al. further teach that the α4β7 Mab rapidly improved stool consistency and the α4β7 integrin represents a novel, potent and organ-specific therapeutic target for the therapeutic modulation of inflammation in the gastrointestinal tract. According to the Office Action, the claims invention differs from the reference teachings only by the recitation of the antagonist is an antibody in claims claims 2 and 12, the antibody is an αEβ7 Mab in claims 3 and 13, wherein the other therapeutic agent is an antibody in claims 22 and 27, and the antibody is an α4β7 Mab in claims 23 and 28.

The Office Action concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the peptide and the pharmaceutically

active compound in the method of treatment taught by '281 patent with αEβ7 Mab taught by the '630 patent and α4β7 Mab taught by Hesterberg et al. in methods of treating and preventing an inflammatory bowel disease, asthma, rheumatoid arthritis, autoimmune diseases and graft versus host diseases as taught by the '281 patent. Further stated in the Office Action is that one of ordinary skill in the art at the time the invention was made would have been motivated to do so because such antibody that modulates adhesion between T lymphocytes (e.g. IELs) and E-cadherin cells are useful for targeting the delivery of therapeutic agents such as an antibody αEβ7, taught by the '281 patent, and targeting α4β7 integrin represents a novel, potent, and organ-specific therapeutic target for the therapeutic modulation of inflammation in the gastrointestinal tract as taught by Hesterberg et al.

Claim 1 is amended herein to recite a method of treating inflammatory bowel disease in a subject, comprising administering to the subject a monoclonal antibody to αEβ7. Similarly, claim 11 is amended to recite a method of preventing inflammatory bowel disease in a subject, comprising administering to the subject a monoclonal antibody to αEβ7.

As stated above by applicants, the '281 patent teaches the administration of an isolated peptide derived from the extracellular domain of E-cadherin, which binds to αEβ7 and inhibits the adhesion between an IEL and E-cadherin. The disclosure of an interaction between αEβ7 and E-cadherin does not mean that administering a monoclonal antibody against αEβ7 would be successful in treating or preventing inflammatory bowel disease. In support of this assertion, applicants provide herewith as Exhibit A, the Declaration of Dr. Eugene C. Butcher, a Professor in the Department of Pathology at Stanford University (curriculum vitae attached hereto), whereby Dr. Butcher declares that it is his belief that although the '281 patent discloses the administration of an isolated peptide derived from the extracellular domain of E-cadherin, which binds to αEβ7 and inhibits the adhesion between an IEL and E-cadherin, this interaction between αEβ7 and E-cadherin is not relevant to the present claims, because E-cadherin is expressed in epithelial cells and is not expressed to any appreciable extent in non-epithelial cells of the gut, such as the lamina propia, where inflammatory bowel disease manifests itself (Strauch et al. "Integrin αEβ7 Mediates Adhesion to Intestinal Microvascular Endothelial Cell Lines Via an E-Cadherin-Independent Interaction" *J. Immunol.* 166: 3506-3514, 2001; Hanby et al.

"Downregulation of E-Cadherin in the Reparative Epithelium of the Human Gastrointestinal Tract" *Am. J. Pathol.* 148:723-9, 1996; Cepek et al. "Integrin αEβ7 mediates adhesion of T-lymphocytes to epithelial cells" *J. Immunol.* 150:3459, 1993; Cepek et al. "Adhesion between epithelial cells and T lymphocytes mediated by E-cadherin and the αEβ7 integrin" *Nature* 372:190, 1994; Karcela et al. "Recognition of E-cadherin on epithelial cells by the mucosal T cell integrin αM290β7 (αEβ7)" *Eur. J. Immunol.* 25:852, 1995; Higgins et al. "Direct and regulated interaction of integrin αEβ7 with E-cadherin" *J. Cell Biol.* 140:197, 1998) (copies attached hereto). Therefore, the suggestion that the interaction between αEβ7 and E-cadherin can be inhibited to treat inflammatory bowel disease is not supported by the longstanding understanding of E-cadherin expression and mechanisms of inflammatory bowel disease. His belief is based on the following scientific facts and observations.

Dr. Butcher states that although E-cadherin has been identified as an αEβ7 ligand, this is not the only ligand for αEβ7. αEβ7, like other integrins, binds to more than one ligand. For example, the I-domain containing integrin, aMb2(Mac 1), binds a wide repertoire of ligands, including ICAM-1, fibrinogen, iC3b, factor X, denatured proteins, neutrophil inhibitory factor, lipopolysaccahride and zymosan. Yalamanchili et al. (*J. Biol. Chem.* 275: 21377, 2000) have shown that the I-domain is required for binding to some ligands and not others. Similarly, another integrin, α4β7, has multiple ligands, including MadCAM-1, VCAM-1 and fibronectin. Monoclonal antibodies have been generated that define unique patterns of inhibition for α4β7 binding to each of its defined molecular ligands (Andrew DP, *J. Immunol.* 153:3847, 1994). Yet another example is the α3β1 integrin which binds collagen, laminin and fibronectin. However, only the binding of α3β1 integrin to fibronectin, not the binding of α3β1 integrin to laminin or collagen, can be inhibited by RGD-containing peptides (Elices, MJ, *J. Cell Biol.* 112:169, 1991). The αEβ7 integrin is distinct from other integrins in containing both an I-domain and an X domain of 55 amino acids. Binding of alphaE to E-cadherin does not appear to involve the X domain and it is believed that the X domain may be involved in interactions with yet unidentified αEβ7 ligands (Higgins et al. J. Biol. Chem. 275:25662, 2000). Therefore, it is well accepted that an inhibitor of a ligand for a particular integrin is not expected to be an inhibitor of all of the ligands which bind to that integrin.

As stated above, it is also known that E-cadherin is not expressed to any appreciable extent in the lamina propia of the gut. Therefore, it is highly unlikely that inflammatory bowel disease is mediated via an αEβ7-E-cadherin interaction. The publication by Strauch et al. ("Integrin alpha E(CD103)beta 7 mediates adhesion to intestinal microvascular endothelial cell lines (HIMEC) via an E-cadherin-independent interaction," *J. Immun.* 166: 3506-3514, 2001) reports that αEβ7 mediates adhesion to intestinal endothelial cells in the lamina propia *in vivo*, via an E-cadherin-independent interaction. Strauch et. al. also suggest the presence of a second ligand for αEβ7 that is clearly distinct from E-cadherin and with a different expression pattern. This reference also showed that a mAb that blocks E-cadherin mediated cell binding to αEβ7, did not block binding of HIMEC to an αEβ7-Fc. Furthermore, HIMEC did not express detectable levels of E-cadherin.

Another reference has suggested that αEβ7 mediates lymphocyte binding to a skin-derived epithelial cell line through an E-cadherin independent interaction (Brown et al. "Mechanisms of binding of cutaneous lymphocyte-associated antigen-positive and alphaebeta7-positive lymphocytes to oral and skin keratinocytes" *Immunology* 98:9-15, 1999). Further evidence that αEβ7 can have a different, E-cadherin independent role in cell homing and inflammation comes from gene expression analysis showing that αEβ7 is expressed on T cell populations outside the intraepithelial area, e.g. in areas that do not contain E-cadherin expressing cells (Gavin M. et al., "Homeostasis and anergy of CD4(+)CD25(+) suppressor T cells in vivo" *Nat. Immunol.*, 3(1):33, 2002; Zelenika D., "Regulatory T cells overexpress a subset of Th2 gene transcripts" *J. Immunol.* 168(3): 1069, 2002; McHugh RS et al., "CD4(+)CD25(+) immunoregulatory T cells: gene expression analysis reveals a functional role for the glucocorticoid-induced TNF receptor" *Immunity* 16(2):311, 2002).

Therefore, it would not be expected that the identification of an inhibitor of E-cadherin binding to αEβ7, would provide an inhibitor for the interaction of αEβ7 with another ligand, such as the ligand involved in inflammatory bowel disease. Although the '281 patent discloses that

administration of an E-cadherin peptide leads to decreased localization of intra-epithelial lymphocytes to the intraepithelial compartment, the '281 patent does not show or suggest that an αEβ7 Mab will inhibit binding of αEβ7 to another ligand or that an αEβ7 Mab will inhibit any activity associated with the interaction of αEβ7 with a non-E cadherin ligand. Furthermore, because E-cadherin is not found at appreciable levels in the lamina propia, it would not be likely that an E-cadherin based mechanism would be successful for treatment of inflammatory bowel disease, and it would not have been obvious, at the time the present invention was made, to target an E-cadherin ligand, e.g. αEβ7, to treat inflammatory bowel disease. Therefore, it would not be obvious to substitute the peptide of the '281 patent with an αEβ7 Mab to arrive at the present invention.

Furthermore, the teachings of Hesterberg et al. regarding α4β7, do not suggest that αEβ7 is involved in inflammation, much less that it should be the target of an anti-inflammatory therapy in combination with α4β7. It was not until the present invention that αEβ7 was identified as a target for the treatment and prevention of inflammatory bowel disease. Thus, therapy comprising an αEβ7 Mab and an α4β7 Mab was not possible until the present invention. Therefore, it would not have been obvious to combine the teachings of the '281 patent, the '630 patent, Baumgart et al. and Hesterberg et al. to arrive at the present invention. Thus, applicants believe that this rejection has been overcome and respectfully request its withdrawal.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $930.00 (three (3) month extension of time fee) is enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

Gwendolyn D. Spratt
Registration No. 36,016

NEEDLE & ROSENBERG, P.C.
The Candler Building
127 Peachtree Street, N.E.
Atlanta, Georgia 30303-1811
(404) 688-0770

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on the date shown below.

Gwendolyn D. Spratt — Date: 3-6-03

Marked-Up Version of Amended Claims
Serial No. 09/856,544

1. (Amended) A method of treating [inflammation] inflammatory bowel disease in a subject, comprising administering to the subject a[n antagonist] monoclonal antibody to αEβ7.

11. (Amended) A method of preventing [inflammation] inflammatory bowel disease in a subject, comprising administering to the subject a[n antagonist] monoclonal antibody to αEβ7.

21. (Ameded) The method of claim 1, further comprising administering [another therapeutic agent] a monoclonal antibody to α4β7.

26. (Amended) The method of claim 11, further comprising administering [another therapeutic agent] a monoclonal antibody to α4β7.